AMENDMENTS TO THE SPECIFICATION

IN THE SPECIFICATION:

Page 1

Before line 1 of the specification, please insert the following new paragraph:

This application is a Divisional of co-pending Application No. 09/807,007, the entire contents of which are hereby incorporated by reference and for which priority is claimed under 35 U.S.C. § 120 which is the national phase of International Application No. PCT/SE99/01784 filed on October 6, 1999. This application claims priority under 35 U.S.C. § 119 on Swedish Application No. 9803393-9 filed in Sweden on October 6, 1998.

Page 5

Please amend the paragraph at page 5, lines 20-21 as follows:

Figure ~~1 shows~~ 1A, 1B, 1C, 1D, 1E, 1F, 1G, 1H and 1I show the genomic sequence of SEQ ID NO:5, wherein exons and introns are designated in the genomic sequence of the novel human patched 2 gene.

The paragraph beginning on page 5, line 22 has been amended as follows:

Figure 2A discloses an amino acid sequence comparison of the human PTCH2 (residues 1-633 of SEQ ID NO:1) (upper lines) and PTCH1 (residues 1-699 of SEQ ID NO:6) (lower lines) sequences.

The paragraph beginning on page 5, line 24 has been amended as folllows:

Figure 2B is a representation of the alternative splicing events (SEQ ID NOS:7, 8, 9, 10, and 11) that result in different C-termini.

Please amend the paragraph starting at page 5, line 28 and ending at page 6, line 3 as follows:

A "label" is a composition detectable by spectroscopic, photochemical, biochemical, immunochemical, or chemical means. For example, useful labels include ^{32}P, fluorescent dyes, electron-dense reagents, enzymes (*e.g.*, as ~~sommonly~~ commonly used in a ELISA), biotin, dioxigenin, or haptens and proteins for which antisera or monoclonal antibodies are available (*e.g.*, the peptide of SEQ ID NO:1 can be made detectable, *e.g.*, by incorporating a radio-label

into the peptide, and used to detect antibodies specifically reactive with the peptide).

Page 7

Please amend the paragraph starting at page 7, line 26 and ending at page 8, line 3 as follows:

The term "target nucleic acid" refers to a nucleic acid (often derived from a biological sample), to which a ~~nucelic~~ nucleic acid probe is designed to specifically hybridise. It is either the presence or absence of the target nucleic acid that is to be detected, or the amount of the target nucleic acid that is to be quantified. The target nucleic acid has a sequence that is complementary to the nucleic acid sequence of the corresponding probe directed to the target. The term target nucleic acid may refer to the specific subsequence of a larger nucleic acid to which the probe is directed or to the ~~ovarall~~ overall sequence (*e.g.*, gene or mRNA) whose expression level it is desired to detect. The difference in usage will be apparent from context.

Page 13

Please amend the paragraph at page 13, lines 1-26 as follows:

In a specific aspect, the present invention relates to the isolated human genomic PTCH2 nucleic acid comprising parts or all of the genomic sequence denoted SEQ ID NO: 5. In the disclosure of the genomic sequence shown in ~~Fig 1~~ Fig 1A, 1B, 1C, 1D, 1E, 1F, 1G, 1H and 1I, the exon/intron structure of the present gene is shown. Further to the exons shown therein, exon 12a and 12b has also been identified, as specifically defined by SEQ ID NO:3 and SEQ ID NO:4, respectively. Interestingly, there is a splice variant that joins exon 12a to a 3' segment of exon 12b with conservation of the intronic GT-AG dinucleotides. Exons 12a and 12b are not variants, but the actual exons of the gene identified by sequencing the corresponding genomic region. (Materials and methods were as described below ~~discribed beloow~~). Accordingly, these findings show that PTCH2 has the same intron/exon structure organization as PTCH1. In another embodiment of this aspect, the present invention relates to a transcript that has skipped only one of the exons 9 and 10 defined in ~~Fig 1~~ Fig 1A, 1B, 1C, 1D, 1E, 1F, 1G, 1H and 1I. In an alternative embodiment, the transcript according to the invention has skipped both of exon 9 and 10. The splice variants of the present gene are discussed in more detail below in the section "Results", all of which are included within the scope of the present invention. This aspect of the invention advantageously

enables design of suitable PCR primers, which in turn enables screening for mutations of all of the coding sections thereof, *e.g.* by SSCP analysis, sequencing, or any other suitable method known to someone skilled in this field. Thus, the novel human PTCH2 gene according to the invention has been localized by radiation hybrid mapping to chromosome 1p32-35 with D1S211 and WI-1404 as closest flanking markers and with an estimated localization 5.5cR from D1S443. This region is often lost by LOH in various different tumor types, such as neuroblastoma, melanoma, breast cancer, colon cancer *etc*. Accordingly, PTCH2 is a candidate for a tumor suppressor gene in this region and the present invention also encompass diagnostic methods based on this new disclosure.

Page 18

The paragraph beginning on page 18, line 8-17 has been amended as follows:

Detailed description of the drawings

Figure ~~1 shows~~ 1A, 1B, 1C, 1D, 1E, 1F, 1G, 1H and 1I show the genomic sequence of SEQ ID NO:5, wherein exons and introns are designated in the genomic sequence of the present human patched 2 gene. However, exons 12a and 12b discussed above are not specifically shown in ~~Figure 1~~ Figure 1A, 1B, 1C, 1D, 1E, 1F, 1G,

1H and 1I, but is instead disclosed as the separate sequences SEQ ID NO:3 and SEQ ID NO:4, respectively. Figure 2A discloses an amino acid sequence comparison of the human PTCH2 (residues 1-633 of SEQ ID NO:1) (upper lines) and PTCH1 (residues 1-699 of SEQ ID NO:6) (lower lines) sequences. Vertical lines indicate identical amino acids, while dots similar amino acids. The PTCH2 sequence presented is composed of the original cDNA clones and of the products of the 5' RACE analysis.

The paragraph beginning on page 18, line 19, has been amended as follows:

Figure 2B is a representation of the alternative splicing events (SEQ ID NOS:7, 8, 9, 10, 11, 12, 13, 14, 15 and 16) that result in different C-termini. In the parotid gland and the colon, the penultimate and the last exon are canonically joined together. In fetal brain however the penultimate exon with part of the 3' intron functions as the terminal exon. The intronic sequence is shown by small letters with the flanking exonic by capital letters. Above the nucleotide sequence, the deduced amino acid sequence is shown, and below is the corresponding sequence of the mouse Ptch2. The conserved intronic dinucleotides are shown by bold letters and the

termination signals are indicated by asterisks. Note the absence of conservation of the position of the termination codons between the mouse and human PTCH2 sequences. The putative polyadenylation signals are also shown in this diagram. The genomic organization was obtained by analyzing BAC clones encompassing the PTCH2 gene.